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Omalizumab versus 'Usual Care': Results from a Naturalistic Longitudinal Study in Routine Care

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Key Words
Allergic asthma · Omalizumab · Pulmonary diseases

Abstract
Background: It is unclear how far the superior efficacy of omalizumab, established in randomized controlled clinical trials of patients with severe allergic asthma (SAA), translates into routine practice and when compared to matched controls. ***Methods:*** New-onset omalizumab-treated (OT) patients with SAA (n = 53) were compared to a matched control group of usual-care (UC) patients (n = 53). Treatment and procedures were naturalistic. Subsequent to a baseline assessment, patients were followed up over at least 6 months with at least two follow-up assessments. Primary clinical outcomes were the number of asthma attacks, persistence of asthma symptoms and degree of control [asthma control test (ACT), Global Initiative for Asthma]. Secondary outcome criteria were quality of life (Euro-Qol 5D) and number of medications. For each outcome we compared within-group effects from baseline to 6-month follow-up as well as between-group effects. ***Results:*** OT patients showed significant improvements in number [effect size (ES) = 0.03] and frequency (ES = 0.04) of asthma attacks as well as asthma control (ES = 0.09), whereas controls revealed no significant improvements in these measures. Further improvements in the OT group were found for 'perceived control always' (ACT, p = 0.006), no impairment (ACT, p = 0.02), reduction of sickness days (p = 0.002) and number of medications needed (p = 0.001). ***Conclusions:*** Substantial beneficial effects of omalizumab, similar to those observed in controlled trials and after marketing studies, were confirmed, particularly with regard to the reduction of asthma attacks, persistence of symptoms, asthma control and reduction of concomitant asthma medications. This study provides a tougher test and generalizable evidence for the effectiveness of omalizumab in routine care.

Introduction

A series of controlled clinical trials has established the superior efficacy of omalizumab in patients with severe allergic asthma (SAA) compared to placebo and standard treatment [1, 2]. Consequently, omalizumab (Xolair; Novartis AG, Basel, Switzerland) was listed with the highest evidence for the effective treatment of uncontrolled al-

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lergic asthma (AA) on treatment step 5 in the Global Initiative for Asthma (GINA, 2007) and in the Asthma Guidelines of the German Respiratory Society [3]. Fairly consistently superior findings were found: a lower incidence and frequency of exacerbations, a reduction of inhaled corticosteroids (ICS), a less frequent need for rescue medication and a reduction of emergency visits, as well as a significant improvement in quality of life [4–7]. Moreover, its safety and tolerability have been previously described [8].

There is evidence that these effects, established in controlled clinical trials, also translate into clinical practice. Molimard et al. [9] reported long-term follow-up data of 147 patients who had had omalizumab prescribed between 2003 and 2006. Compared with the year before treatment, the percentage of patients without exacerbations doubled, emergency visits (–69%) and hospitalizations (–53%) decreased, 25.6% of patients stopped using or lowered the dose of ICS, and 48.1% reduced or discontinued maintenance on ICS. Korn et al. [10], in a postmarketing surveillance trial of 280 patients with severe persistent allergic asthma, described effects in terms of daily symptoms (–76%), exacerbations (–82%, hospitalizations (–78%), control status and quality of life [Mini Asthma Quality of Life Questionnaire (AQLQ) increase: 2.9–4.5]. Bousquet et al. [1] performed a pooled analysis of data from the INNOVATE study, pointing out that patients being treated with omalizumab showed a significant decrease in asthma exacerbations (40–50% decrease vs. control), fewer severe exacerbations (40–70% vs. control) and significantly fewer emergency visits (30–60% compared with controls) [11]. Ayres et al. [4] compared 206 patients with omalizumab therapy and 106 patients with standard treatment. They reported a significant reduction of asthma deterioration-related incidents (course of systemic corticosteroids or antibiotics for ≥ 2 days, ≥ 2 missed school/work days) in patients treated with omalizumab (reduction 49.6%), and significantly fewer asthma exacerbations (reduction 60.8%). Moreover, omalizumab treatment (OT) improved lung function parameter (FEV_1) more significantly than standard treatment.

To summarize, as controlled studies, these naturalistic and real-life studies have typically found similar promising effects. However, considerable caution is warranted given the weaknesses of uncontrolled naturalistic observational studies. Further, it should be noted that none of the available real-life studies had implemented a control group with standard treatment. It is unknown what the natural course of patients would have been in the same time period under conventional routine treatment.

To avoid most of these weaknesses, we present a more sophisticated approach to estimate the effects of omalizumab under real-life conditions. To eliminate systematic selection effects as far as possible, sampling of patients is based on a nationwide representative patient population, recruited as part of a previous clinical-epidemiological study [12]. From the same patient population we also selected matched controls without omalizumab treatment. This allowed us to estimate the reduction in each group, as well as to compare the effects in both groups. Our aims were:

(1) To describe in a prospective naturalistic matched-control group design the effects of add-on omalizumab treatment over a period of 6–8 months in 106 subjects with uncontrolled SAA. One group comprising 53 patients received OT and a group of 53 carefully matched 'usual care' (UC) controls went without omalizumab. Outcome variables were: mean number of asthma attacks, frequency of asthma symptoms, degree of asthma control (primary) and quality of life (secondary).
(2) To compare, over a period of 6–8 months, the effects of treatment with omalizumab to the controls to test whether OT outcomes were superior to UC.

Materials and Methods

This prospective-longitudinal cohort study was part of the Severe Asthma Patients Needs Study (sap-NEEDs; Severe Allergic Asthma: Prevalence and Current Treatment Needs), described elsewhere in detail [12]. Briefly, sap-NEEDs was a 3-stage, nationwide, cross-sectional (stages 1 and 2) and prospective (stage 3) clinical-epidemiological study in a nationally representative sample of 756 pulmonary specialists and their patients (stage 1). In stage 2 of sap-NEEDs, a random sample of 572 patients (response rate: 68%) recruited from a random subset of 146/756 settings underwent a comprehensive clinical assessment supplemented by a patient questionnaire. This contained questions regarding patient characteristics, symptomatology, treatment and established scales including the AQLQ [13], the generic Euro-Qol 5D (EQ5D) questionnaire [14], the Asthma Control Test (ACT) [15] and mental health status scales (CIDI-SF) [16]. From this stage-2 database (total of 572 patients with allergic asthma), patients diagnosed with a stage III and IV asthma severity according to NVL ('Nationale Versorgungsleitlinie Asthma', i.e. National Guidelines for Diagnosis and Treatment of Asthma, n = 339) were eligible and targeted as potential participants for the prospective-longitudinal naturalistic cohort study dealt with in this paper. At the time the study was conducted, the NVL guidelines were identical to GINA in terms of grading the severity of asthma. However, it did not include the therapy staging of GINA; this was adopted only after the study had been completed. In order to reflect this change and to be consistent with international standards, we decided to use GINA criteria.

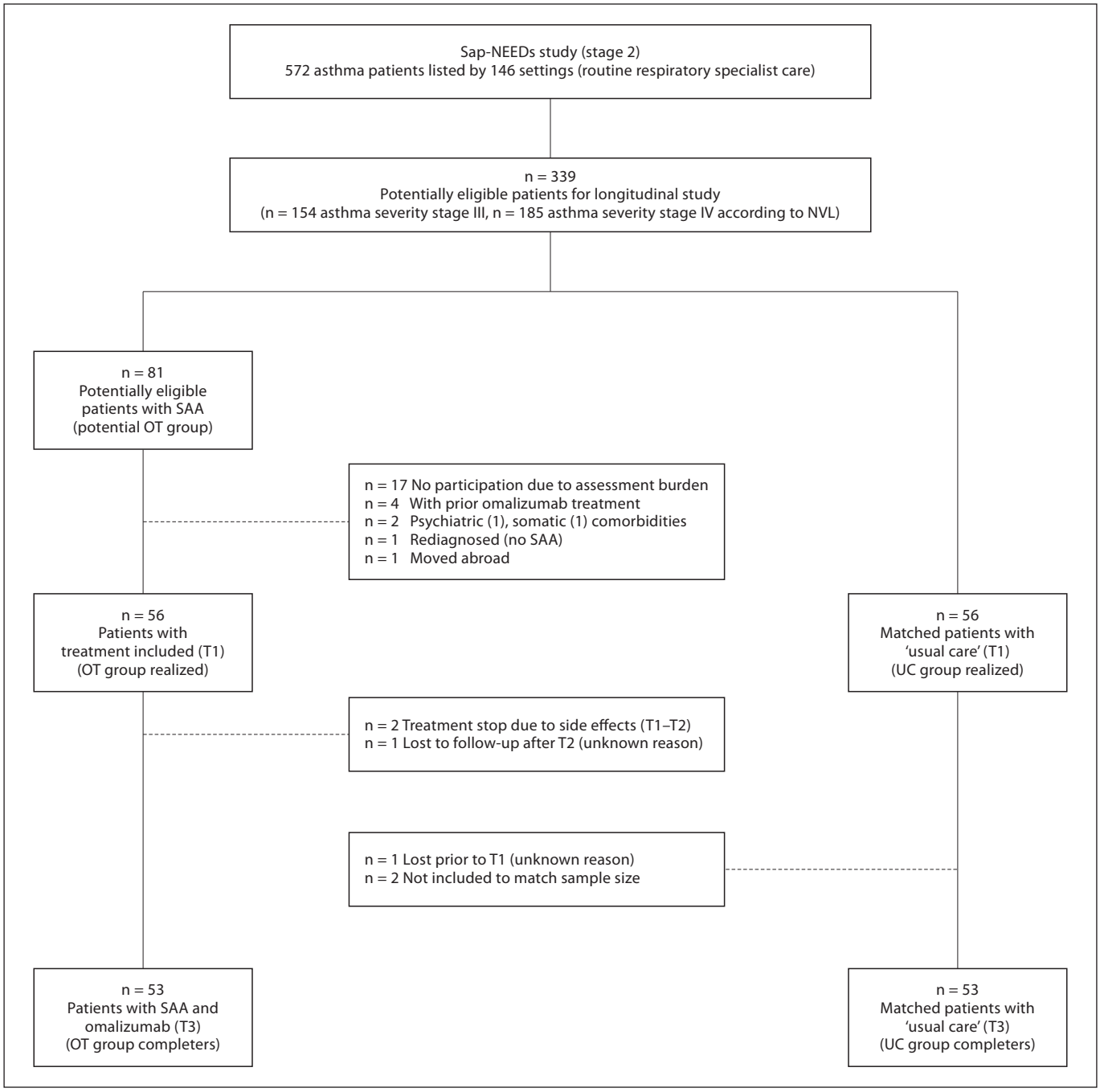

Fig. 1. Study design.

Design and Patient Groups

The design of the cohort is displayed in figure 1. The selection of patients for this longitudinal component was based on a complete listing of all patients with SAA together with a clinical characterization made by their treating physicians, obtained from stage 2 of the study [12]. The patients sample was based on findings from the stage 2 questionnaire that asked the treating physician what type of treatment (including omalizumab) he/she either currently administered to this patient or considered administering in the near future. This applied for 81 patients. If these patients met the inclusion and exclusion criteria, the physician was requested to ask for informed consent for the study proce-

dures (potential OT group). The UC group selected by the study center was also based on the available stage-2 data, by matching patients that had biosocial and clinical characteristics similar to those of patients in the OT group (same inclusion and exclusion criteria).

Inclusion and Exclusion Criteria

All patients had to meet the diagnostic study criteria for uncontrolled SAA (according to GINA). General inclusion criteria were: written informed consent, age 16–75 years, severe persistent allergic asthma, positive skin test or in vitro reactivity to perennial aeroallergen, reduced lung function [(FEV_1) <80%, peak expiratory flow 60–80% or daytime variability >30%], frequent daytime symptoms and severe exacerbations. Exclusion criteria were: prior OT, other severe somatic and psychiatric conditions that required continuous medication treatment or frequent consultations and conditions that would make regular assessments of the patients impossible due to logistical or ethical reasons (e.g. language problems, acute pain and suffering).

Omalizumab Treatment Group

Of the 81 potentially eligible patients approached, 17/81 declined participation, mostly because of the associated assessment burden, and 8 (8.6%) dropped out because they did not meet the study criteria. Four had had previous OT, 1 had end-stage cancer and another had severe depression (a suicide attempt). One patient did not meet the diagnostic criteria of SAA and 1 was about to move abroad. So 56 patients were enrolled in the study; 3 stopped taking omalizumab after 2–5 weeks of observation (discontinued by the treating physician because of adverse reactions or side effects). So the OT group finally comprised 53 patients. The dosage of omalizumab was determined according to the treatment guidelines, based upon a patient's body weight and IgE levels.

'Usual Care' Control Group

The same inclusion criteria applied for this group, except that for these patients no OT was considered, i.e. 'usual care' refers to step 1–5 of the GINA scheme but without OT. We matched 56 control subjects to the original 56 omalizumab patients (see below). Matching started with biosocial characteristics and included clinical characteristics (e.g. smoking status, FEV_1, number of allergies, duration of prior treatment and exacerbations over the past 12 months) to optimize the match (table 1). All patients agreed to participate. One dropped out before the first follow-up assessment. To obtain equal group sizes, we restricted the analyses to 53 patients who were matched to the patients in the OT group (this exclusion had no effects on the results).

Procedure

As shown in figure 1, patients were followed up by independent clinical monitors with 3 assessments (T1–T3) over at least 6 months. The physician again completed a standardized clinical appraisal for each patient. All patients completed an exam prior to entering the study consisting of a standardized clinical assessment and a self-report questionnaire. Controls continued their UC treatment without omalizumab. The OT group started their treatment subsequently. Data are presented for both groups with their baseline (T1), intermediate (T2 at 2–3 months) and final follow-up (T3 at 6–8 months) assessments. Out of 106 patients, 104 completed all the assessments. Two omalizumab patients stopped their medication between T1 and T2 due to clinical reasons (side effects and tolerability). None of the 53 controls dropped out.

Baseline and Follow-Up Assessment

The baseline and follow-up assessments consisted of a standardized, interviewer-based assessment of the following variables, which served as outcome measures: number of patients with asthma attacks, mean number of asthma attacks and number of patients with daily and frequent day/night symptoms during the past 4 weeks were assessed with the Asthma Symptom List and the Asthma Trigger Inventory [17]. The frequency of asthma symptoms during the past 4 weeks was assessed with a corresponding ad hoc item which could be answered by the patient as 'daily (permanently)', 'daily (frequently)', 'not daily, but x times per week' or 'none'. In this paper, patients who reported 'daily (permanently)' or 'daily (frequently)' were pooled as having 'daily symptoms'. Asthma control was assessed with the ACT [18]. Here, a patient was classified as having 'partially controlled' asthma when he/she scored 20–24 (out of 25) or 'no control' when he/she scored ≤19.

Quality of life was assessed by the EQ-5D using the proportion of patients with 'any problems in usual activities' and 'any discomfort due to symptoms' as core indicators [14]. The clinician also rated the following variables: exacerbations during the past 4 weeks, lung function (current peak expiratory flow), number of emergency visits (hospitalizations, ER visits or need of ventilation) and, performed a final appraisal of efficacy and tolerability upon conclusion of T3.

Analyses

Baseline characteristics of the OT and UC group were compared by a χ^2 test for nominal data and a Student t test for interval data. The UC group was matched by propensity score [19]. The propensity score was the probability to be in the OT given the matching variables. Each subject in the OT group was matched to the subject with the closest propensity score from the UC sample. Power analyses were conducted for estimating the statistical power for the applied test procedures in our sample [20]. Changes in the outcome variables from T1 to T2 and T3 were reported as change in percentage for nominal data and change in the mean for interval data. The within-group changes were assessed by paired t tests and a paired sample proportion test. The standardized change (effect size) from T1 to T3 was estimated by the mean difference divided by its pooled standard deviations (SDs). The effect size provides a comparison of changes for different outcome variables. Regarding the primary aims and the design of the sapNEEDs project, we analyzed the in-group differences for the change of T1–T3 by a bootstrap test for ratio, applying 5,000 bootstrap replications. The treatment effect at T2 is reported as ratio with the reference group UC. Missing observations in outcome variables due to item nonresponse were imputed by the last-observation-carried-forward approach. A sensitivity analysis considering only complete cases did not reveal different study results. Standard errors were robustly estimated. Statistical significance is based on $p < 0.05$. All statistical analyses were performed using STATA 11.

The local ethics committee reviewed and approved the study protocol (9 May, 2008, ref. EK 43032008).

Table 1. Baseline characteristics of the study sample of 106 patients

	OT group	UC group	p value[a]
Number of patients	53	53	
Mean age ± SD (range), years	48.3 ± 13.7 (16–72)	51.9 ± 15.9 (19–74)	0.212
Sex, %			
Male	50.9	50.9	1
Female	49.1	49.1	
Professional status, %			
Employed	52.2	40.4	0.371
Retired	34.8	51.9	
Seeking work	8.7	5.8	
Homemaker	4.4	1.9	
Mean years of schooling ± SD	11.4 ± 3.1	10.8 ± 2.5	0.318
Smoking status, %			
Ex-smoker	38.3	32.7	0.836
Current smoker	6.4	7.7	
Mean serum total IgE ± SD, I.E./ml	605.1 ± 793.5	374.2 ± 539.2	0.141
Mean FEV_1 %[b] ± SD	67 ± 23	62 ± 19	0.262
Mean peak flow reversibility ± SD	24.1 ± 42.0	26.9 ± 48.0	0.891
Mean vital capacity %[b] ± SD	85 ± 22	86 ± 23	0.808
Mean duration of allergic asthma ± SD, years	19.7 ± 14.6	24.1 ± 17.8	0.231
Mean duration of prior treatment ± SD, years	20.3 ± 14.8	21.8 ± 15.6	0.661
Mean number of exacerbations in the last 12 months ± SD	3.1 ± 2.6	4.8 ± 7.9	0.266
Mean number of severe exacerbations in the last 12 months ± SD	1.8 ± 1.0	3.7 ± 5.5	0.175
Mean number of emergency visits in the last 12 months ± SD	0.7 ± 1.3	1.1 ± 3.6	0.460
Concomitant medication, %	96.2	90.6	0.241
Systemic corticosteroids, %	66.0	39.6	0.006
LABA, %	71.7	62.3	0.302
SABA, %	73.6	83.0	0.239
Detected allergens, %[d]			
Birch	53.3	53.1	0.979
Grass pollen	56.6	55.1	0.969
House dust mites	60.0	38.8	0.040
Cat dander	53.3	44.9	0.414
Alternaria	13.3	14.3	0.894
Cladosporium	13.3	4.1	0.108
Food	15.5	18.4	0.717
Other	37.8	34.7	0.756

Continuous data are expressed as means ± SD (range); nominal data are given as percentages.
[a] χ^2 test (nominal data) or t test (interval data) were performed. [b] Percentage of predicted standard value. [c] Asthma severity by the NVL. [d] Documented by the treating physician (skin prick test).

Results

Patients

A summary of the baseline characteristics of both groups is reported in table 1. Overall, the groups are relatively well balanced regarding most variables, revealing significant differences only with regard to the higher rate of systemic corticosterioids in the OT group (66 vs. 39.6%, p = 0.0006). Half of the sample was female; mean age was 48.3 and 51.9 years, respectively. They did not differ with regard to duration of illness (19.7/24.1 years, p = 0.231), duration of prior treatments (20.3/21.8 years, p = 0.661), and the frequency of concomitant asthma medications (96.2/90.6%, p = 0.241).

Table 2. Comparison of treatment outcomes in patients of the OT group (n = 51) and matched controls (UC, n = 53)

	OT group				UC group				Between-group effect T1–T3
	change[a] T1–T2	change[a] T1–T3	within-group effect T1–T3		change[a] T1–T2	change[a] T1–T3	within-group effect T1–T3		
			p value[b]	effect size[c]			p value[b]	effect size[c]	p value[d]
Number of patients with asthma attacks	–55.6	–50.0	0.028		–54.5	–40.9	0.019		0.344
Mean number of asthma attacks	–53.8	–72.9	0.031	0.40	–23.9	–22.2	0.592	0.09	0.100
Number of patients with daily or frequent asthma symptoms	–22.5	–17.5	0.042		–5.0	0.0	1.000		0.104
Asthma control									
ACT	6.5	5.9	0.265	0.18	11.1	0.6	0.886	0.04	0.801
Patients with partial/no control	–14.9	–10.6	0.096		–8.9	–6.7	0.261		0.215
Impairment: never	150.0	80.0	0.019		100.0	30.8	0.289		0.795
Emergency medication: rarely/never	14.3	28.6	0.135		17.4	13.0	0.444		0.952
Short of breath: rarely/never	5.0	–15.0	0.371		0.0	–20.8	0.168		0.688
Perceived asthma control: always	500.0	300.0	0.006		157.1	57.1	0.209		0.872
Mean generic quality of life (EQ-5D)	4.0	2.3	0.543	0.14	1.8	0.6	0.839	0.01	0.733
Any problems in usual activities	0.0	–47.6	0.010		–23.8	9.5	0.598		0.006
Any pain/discomfort	–35.7	–21.4	0.110		–18.8	–18.8	0.159		0.436

Reference group is UC controls; ratio and 95% CI estimated by a general linear model.
[a] Change is change in % from T1 value.
[b] Paired t test (interval data) or paired sample proportion test (nominal data) were performed.
[c] Effect size is the standardized mean difference, only indicated for continuous measures.
[d] Between-group effect of change T1–T3 determined by a bootstrap test for ratios.

Comparison of Treatment Outcomes within and between Groups

Table 2 provides a summary of the primary outcome measures for within-group changes as well as between-group differences. Overall, patients in both comparison groups showed substantial and significant improvements expressed as % reductions in most of the outcome measures.

Notable exceptions were the lack of a significant improvement in total ACT score for both groups (fig. 2a). However, significant improvements were observed in some of the subscores in the ACT (fig. 3).

Number of Asthma Attacks and Symptoms Score

As shown in figure 4a, the proportion of patients with at least one severe asthma attack in the past month was reduced from baseline 35.9 to 17% at T2 and 18.9% at T3 in the OT group (p = 0.028). Similarly, the mean number of attacks and exacerbations (fig. 4b) was significantly (p = 0.031) reduced from a mean at baseline of 4.0 (SD 9.6) to 2.1 (5.5) at T2 and 1.1 (SD 3.0) in the whole group, and from 11.2 (SD 13.5) to 7.1 (SD 7.6) among those with at least one exacerbation. This finding is largely due to a substantial increase in patients who became completely free of exacerbations. At T3, 43 (81.1%) patients reported no more exacerbations during the past month (data not shown). In the control group, a similar pattern emerged with a significant (p = 0.019) reduction of the number of patients without attacks; however, the reduction of the mean number of attacks in the total sample and among those with attacks was not significant (p = 0.593).

There was some, though insignificant, reduction of symptom frequency and persistence in the past month for both groups. In the OT group the mean symptom score declined from 4.9 (SD 3.6) at baseline to 4.2 (SD 3.9) at T3 (p = 0.151), and in the control group from 5.0 (SD 4.0) to 4.8 (SD 3.8) at T3 (p = 0.734) (data not shown). It is, however, noteworthy that patients in the OT group versus patients in the UC group revealed a significant reduction in the number of patients with daily symptoms (from T1: 84.0 to 69.2%; p = 0.042), whereas the controls did not (T1: 75.5%, T3: 75.5%; p = 1.00) (fig. 2).

Asthma Control According to ACT

The proportion of patients with 'no control' and 'partial control' was reduced in the OT group (T1: 94.2%, T2: 78.2%, T3: 81.1%), constituting a significant reduction

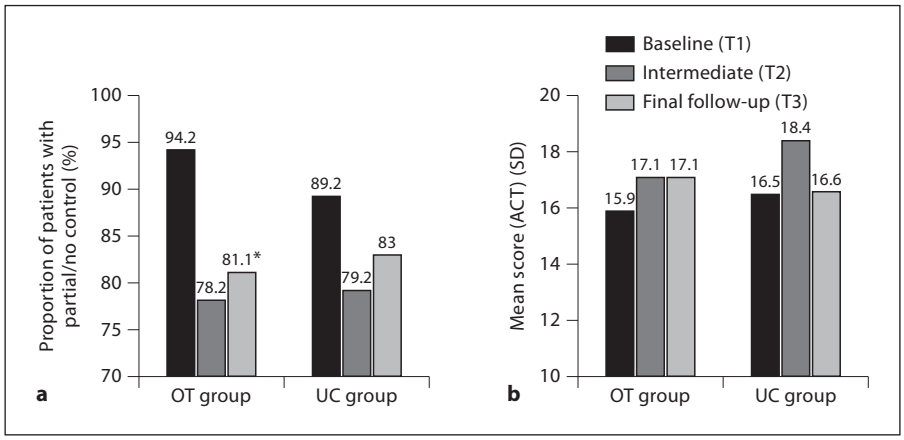

Fig. 2. a Proportion of patients with partial or no control according to the ACT. **b** Mean ACT scores in 53 patients with OT or treatment as usual (UC group, n = 53). * $p < 0.05$.

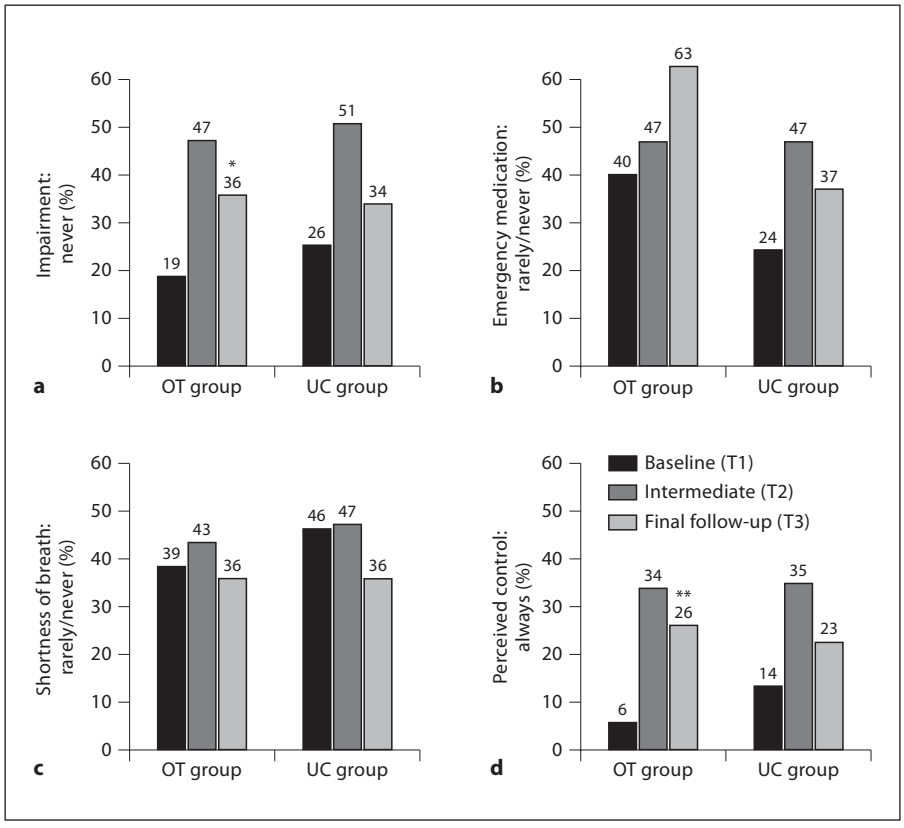

Fig. 3. Domains of the ACT for the past 4 weeks from T1 to T3 in 53 patients with OT or treatment as usual (UC group, n = 53). * $p < 0.05$, ** $p < 0.01$.

from baseline to T2 ($p = 0.024$) and to T3 ($p = 0.049$). In contrast, the reduction in the UC group was less pronounced and was insignificant ($p = 0.112$ and $p = 0.261$), particularly due to a worsening of control at T3 (fig. 2a). No significant improvement was observed when regarding the ACT mean score for both groups (fig. 2b).

This is despite the fact that, as assessed by ACT, the proportion of patients reporting no impairments due to asthma in the past 4 weeks increased significantly ($p = 0.019$) in the OT group (19% at baseline to 47% at T2 and 36% at T3). Further, the proportion of patients reporting being able to 'always' control their asthma increased from 6 to 34% (T2) and 26% ($p = 0.006$). These effects were less pronounced (effect size: OT group 0.35 and 0.51 vs. 0.18 and 0.24 in the UC group) and were not significant in the control group.

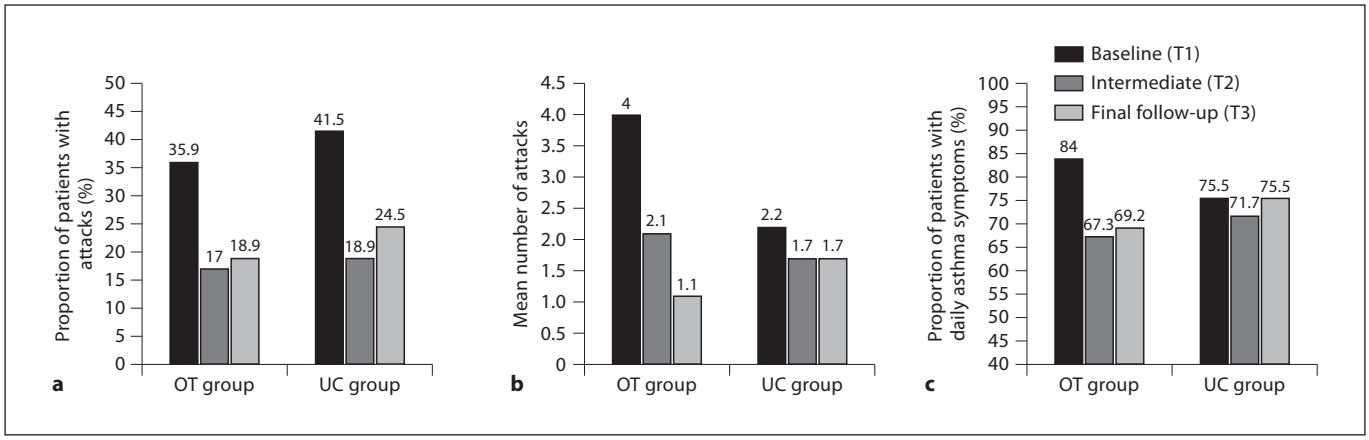

Fig. 4. a, **b** Reductions of severe asthma attacks in the past 4 weeks from baseline to T3 follow-up. **c** Proportion of patients with daily or frequent asthma symptoms in the past 4 weeks from baseline to T3 follow-up in 53 patients with OT or treatment as usual (UC group, n = 53).

Emergency Medication and Treatment

At baseline, 20 out of 53 patients reported at least one emergency visit in the past month. This number was reduced to 4 at T2 and 9 at T3 in the OT group, which constitutes a significant improvement (62%, p = 0.012), and from 11 at T2 to 5 at T3 in the UC group (not significant, p = 0.709), respectively. This is consistent with the ACT rating of needing 'rarely or never reliever medication'. The proportion of patients increased from 40% at baseline to 47% at T2 and 62.8 at T3 in the OT group (p = 0.091) compared to the nonsignificant change from 24, 47 and 37% in the UC group (p = 0.444).

Quality of Life

Although patients in the OT group reported significantly fewer reductions in their limitation of everyday activities from T1 (41.5%) to T3 (20.8%, p = 0.0006), and in the UC group there was no change (38.5 at T1 and 41.5% at T3), we observed no significant change in the EQ-5D generic total score regarding quality of life. The pre- and post-treatment EQ-5D value in both groups approached very closely the level of healthy controls; thus, there was no room for further improvement. Neither group revealed substantial changes nor were there substantial differences between groups.

Concomitant Asthma Medication

Table 3 displays the change of concomitant asthma medication across T1–T3 in the OT group and in the UC group, respectively. Overall and for most medication classes, substantial and mostly significant reductions are apparent for the OT group, whereas changes for the control group were less pronounced. Noteworthy between-group differences were found for long-acting beta agonists (LABA; p = 0.063), anticholinergics (p = 0.065, data not shown), ICS (p = 0.029) and leukotriene antagonists (p = 0.054).

At T1, 68.6–72.5% of all patients in the OT group were treated with systemic glucocorticoids, LABA and short-acting beta agonists (SABA) (39.6–83.0% in the UC group). The data reveal that there was a significant reduction of all three agents in the OT group at T3. At T3, a further intake was necessary for 60% fewer patients than at T1 and 75.7% fewer patients had to continue the intake of LABA. The reductions were less pronounced in the UC group and became significant for LABA only ($p < 0.001$, effect size 1.14). It should be noted, however, that a significant within-group-effect was found in the UC group while no significant change was detected in the OT group with regard to ICS. Significant between-group-effects from T1–T3 were found for the ICS treatment ($p < 0.05$).

Discussion

The results of this naturalistic study in routine specialty care provide prospective-longitudinal evidence of the effects of OT in SAA patients. The strengths of this paper are the reliance on a representative sample of patients in respiratory care, the minimal selection effects and the incorporation of carefully matched controls. Thus, these design features could be regarded as a consid-

Table 3. Concomitant medication in 53 OT patients and matched controls (UC, n = 53)

	OT group				UC group				Between-group effect T1–T3 p value[c]
	T1	change[a] T1–T2	change[a] T1–T3	within-group effect T1–T3 p value[b]	T1	change[a] T1–T2	change[a] T1–T3	within-group effect T1–T3 p value[b]	
SABA, %	70.6	−11.1	−25.0	0.038	62.3	−9.1	−15.2	0.255	0.991
LABA, %	72.5	−75.7	−75.7	0.000	83.0	−61.4	−59.1	0.000	0.063
Systemic glucocorticoids, %	68.6	−42.9	−60.0	0.000	39.6	−23.8	0.0	1.000	0.193
ICS, %	86.3	0.0	6.8	0.322	88.7	−10.6	−14.9	0.018	0.029
Leukotriene antagonists, %	39.2	−30.0	−20.0	0.252	22.6	−25.0	−33.3	0.209	0.054

Reference group is UC; ratio and 95% CI estimated by a general linear model.
[a] Change is change in % from T1 value.
[b] Paired t test (interval data) or paired sample proportion test (nominal data) were performed.
[c] Between-group effect of change T1–T3 determined by a bootstrap test for ratios.

erably tougher test of the effect of omalizumab than those in previous studies [1, 4, 9, 10, 21].

What Our Data Reveal

Patients with SAA showed substantial improvement on OT in almost all the indicators considered. The effect size appears to be in the same range as in previous real-life naturalistic studies [9, 10].

There was also a considerable improvement in the UC group. Thus, both treatment groups showed significant improvement in most outcome measures examined. The improvement in the control group is not surprising, as these patients appear to have also received a very intensive treatment, the important difference being that they did not receive omalizumab.

Consistent with earlier studies, on OT there was a significant reduction of medication (relevant for asthma control) and a substantial reduction of asthma attacks and exacerbations. Moreover, substantial improvements were found in the degree of the perceived control and perceived impairment experienced by the patients in everyday life due to their disease.

However, there was neither a strong nor a statistical overall effect in the ACT as one primary outcome measure, nor could we demonstrate a consistent improvement in quality of life. Despite the finding that effect sizes and % improvements in all outcome measures were typically larger and statistically significant only in the OT group, our at-first-sight puzzling failure to demonstrate a clear superiority of omalizumab in the between-group comparison by means of the ACT score can be attributed to a combination of several factors. First, the most prominent effect of omalizumab is a reduction in exacerbations, confirmed in our study. However, the study period of 6–8 months might have been too short to detect significant differences in exacerbations. Other improvements due to omalizumab primarily measured by the ACT score might be not as prominent. Second, despite similar improvements in effect sizes in this study when compared to others, the ACT might not be responsive enough for such changes. The ACT was developed and validated as a screening tool for asthma control state and not for measuring treatment effects. Alternatively, despite initial power calculations based on previous naturalistic study findings, our study was insufficiently powered to detect significant differences in ACT scores. Third, and probably most important, although our SAA patients improved under effective treatment, they will rarely achieve high (controlled) ACT scores. There was little room for score changes in this patient population compared to initially severe asthma patients with an excellent response to low-dose ICS treatment (treatment step 2).

Similarly, the failure to demonstrate a significant effect in quality of life might be due to a combination of the fairly normal mean generic quality of life of allergic-asthma patients treated in the health care system that we detected and the lack of change sensitivity in this upper range. It should be noted that we considered the use of asthma-specific quality-of-life instruments, which turned out to not be feasible for logistical reasons. The AQLQ is an option to measure quality of life in patients with severe asthma forms and also is suitable for retest purposes. However, as it consists of 32 questions, each of

which has to be answered on a 7-point scale, its feasibility and acceptability for follow-up assessments were found to be restricted because of the associated time burden. We therefore used a considerably shorter instrument to evaluate the generic quality of life at the expense of not having fine-graded disease-specific information that would have been available from the AQLQ.

It is important to understand which factors drive the decision of the respiratory specialists and the not-controlled SAA patients about whether or not to treat with omalizumab. The symptoms of allergic asthma are believed to be due to an inflammatory process, where IgE-mediated events are thought to play a crucial role [22, 23]. By almost eliminating serum free IgE levels, omalizumab has been shown to provide a specific method to treat this condition effectively, with results that are superior to standard treatments in SAA patients with inadequate disease control [24, 25].

One has to keep in mind that the selection of patients in both groups was based on an epidemiological sampling strategy (as described in [12]) and a comprehensive clinical patient assessment by the treating physician. Thus, the selection of patients with a prospective OT in our study was based entirely on the clinician's appraisal and the respective information coded in the standardized assessment forms. As previously reported, we found no indications for selection bias in the preceding stage II component of our study program [12] (from where stage III patients were taken), and – with one exception (systemic corticosteroids) – there were no noteworthy differences between the 2 patient groups (with and without OT treatment). However, given the complete reliance on the data supplied by the treating physicians and the lack of independent information, more subtle selection effects cannot be entirely excluded. Another possible limitation in the data might be caused by the relatively short observation period of 6 months, which was chosen for economic and logistical reasons (study budget and additional burden for the participating physicians and patients).

In the noninterventional study, one can speculate why the matched control patients were not treated. Several reasons are possible: The IgE levels in the control group were higher, thus more patients could have exceeded the maximum approved dose (375 mg every 2 weeks at the time of the study; today doses as high as 600 mg every 2 weeks are even approved). The systemic steroid dose was significantly higher in the OT patients. It is likely that the respiratory specialists targeted such patients expecting a reduction in the systemic steroid dose. Omalizumab in Germany is fully reimbursed and financial or social aspects do not play any role in its prescription, thus making the 2 groups even more comparable.

To conclude, the substantial beneficial effects of omalizumab, similar to those observed in controlled trials as well as in post-marketing surveillance studies, were confirmed, particularly with regard to the reduction of asthma exacerbations and attacks, the persistence of asthma symptoms, asthma control and the reduction of concomitant asthma medications. The failure to show a substantial and consistent improvement in the generic and some of the asthma-related quality-of-life measures may be attributed to a lack of sensitivity of the instrument used. It should also be noted that, as sap-NEEDs was a naturalistic study conducted in the daily routine care of pulmonary specialists, we did not implement comprehensive instruments to assess therapy response as is customary in randomized controlled trials. However, our results indicate a substantial improvement in the condition of patients and it is unlikely that physicians would continue a therapy strategy that turns out to be ineffective. Overall, this study provides a tougher test than previous investigation by comparing the omalizumab performance against adequately managed standard treatment, thus adding further evidence to the considerable benefit of this new treatment option.

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